Objection is made to claims 24-31 under 37 CFR 1.75(c). Claims 24-31 are cancelled without prejudice to reduce issues.

Claims 1 and 24-31 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Kermode.

The present invention is directed to the anti-inflammatory properties of f-Met-Leu-Phe-Phe. These anti-inflammatory properties include **inhibition** of mast cell degranulation; **reduction** of adhesion, migration and aggregation of lymphocytes, eosinophils and neutrophils to a site of inflammation; **inhibition** of the release of cytokines; **inhibition** of the release of histamines; **inhibition** of the release of leukotrienes; wherein the inflammation is due to asthma, arthritis and anaphylaxis. Applicants teach that the **anti-inflammatory** properties of f-Met-Leu-Phe-Phe are highly effective and are desirable for the treatment of such disorders. Dose ranges and pharmaceutical compositions for the anti-inflammatory effects of f-Met-Leu-Phe-Phe are thoroughly discussed in the specification, see pages 11-15 and in the Examples.

Kermode et al teach that chemotactic formyl Met peptides trigger biological responses of neutrophils which play a major role in the body's defense mechanism against infectious microorganisms. The reference teaches that f-Met-Leu-Phe-Phe binds to both high and low affinity receptors of rabbit neutrophils ***in vitro***, is a powerful mediator of rabbit neutrophil degranulation as measured by β-glucosaminidase release ***in vitro***, and is a potent chemotactic agent for rabbit neutrophils ***in vitro***. The teachings of Kermode are in stark contrast to applicant's

teachings wherein the applicants teach that f-Met-Leu-Phe-Phe **inhibit** all of the above responses and f-Met-Leu-Phe-Phe would be desirable for use in the treatment of disorders where the inflammatory response plays a role such as in arthritis, asthma. Based on the properties of f-Met-Leu-Phe-Phe as taught by Kermode et al, it would not have been obvious to anyone of ordinary skill in the art to use the present composition in a pharmaceutically acceptable carrier for the **downregulation** of the inflammatory response, i.e., as an anti-inflammatory agent.

Examiner states that:

> The knowledge that formyl peptides stimulate various functions of neutrophils which constitute defense reaction to infectious microorganisms would be a sufficient motivation to an artisan to apply such an agent as a pharmaceutical under conditions when therapeutic stimulation of such a defense reaction is required.

Applicants teachings do not relate to the protective cellular responses induced by microorganisms in which an inflammatory response is desirable. Rather, Applicants discovered the unexpected and surprising use of **anti-inflammatory** properties of f-Met-Leu-Phe-Phe ***in vivo*** that are useful for the **downregulation** of the inflammatory response in disorders where the inflammatory response is **destructive**. Thus the disclosure of Kermode et al does not teach or anticipate the present invention.

Examiner states that the, "in the Declaration filed 04/00 the effect of the claimed composition is demonstrated only as an inhibitor of inflammatory effect

caused by another f-Met peptide, fMLP." That is a surprising and unexpected effect of the present invention.

The examiner also questions an absence of a showing of the effect of fMLPP alone and suggests that such absence is not surprising because fMLPP alone would be "pro-inflammatory." Applicants disagree strongly with the examiner's suggestion. Indeed, Applicants believe that one skilled in the art would conclude from the showing already made that fMLPP has a strong anti-inflammatory effect.

However, to satisfy the examiner's question, experiments were coinducted under the supervision of Dr. Clagett and the results are presented in the attached Declaration of James Clagett. The declaration shows the effects of HK-X (fMLPP) both alone and in conjunction with fMLP in the mouse model. Briefly, (1) 200 µg of fMLP alone; (2) 200 µg of HK-X alone; (3) 200 µg of fMLP and 200 µg of HK-X together; and (4) as a control the vehicle (4% DMSO in Tyrode's solution) were injected subcutaneously into the dorsum of mice feet. The results show (a) that fMLP alone induced a potent chemotactic response, that by itself HK-X was **not** chemotactic and (b) that HK-X **inhibited** the chemotactic effect of fMLP when HK-X and fMLP were administered together.

Therefore, HK-X mechanism of action functions at the **earliest** stage of inflammation by **inhibiting** the recruitment of inflammatory cells. A second important property of HK-X is that it also **inhibits** the action of a potent chemotactic agent. Accordingly, applicants respectfully submit that Kermode et al, does not teach or

suggest the invention of claims 1, 24-31 and thus, the applicants request that this rejection be withdrawn.

Pursuant to Examiner's comments, "[w]here the claimed and prior art products are identical or substantially identical in composition, a prima facie case of either anticipation or obviousness has been established."

Applicants respectfully disagree for the following reasons. First, the statement presumes no surprising and unexpected results. However, as can be seen from the evidence in the record, the claimed invention has an effect contrary to the teachings of the prior art. It is difficult to find better evidence of a surprising and unexpected result.

Further, neither the **action** of a chemical composition *in vivo,* nor the **reaction** of an individual to that particular chemical composition can be anticipated or made obvious even though the chemical composition and properties of the drug "are inseparable". The immune system is a highly complex, dynamic, intertwined and interlinked system that one cannot predict the action of a certain composition. For example, the composition of penicillin and its properties are well known, however, a person allergic to penicillin will experience anaphylaxis and even death. Whereas, a person who is not allergic to penicillin will benefit from the penicillin and will not experience such undesirable effects. Thus, even though the chemical composition and its properties are known, a *prima facie* case of either anticipation or obviousness

cannot be established when a chemical composition is administered to a living creature.

In the present case, the properties of the claimed composition *in vivo* were not known. Those properties were discovered by Applicants and were contrary to expectations of those skilled in the art.

The examiner continues to suggest that it would be obvious to apply a formyl peptide as a pharmaceutical under conditions when therapeutic stimulation of functions of neutrophils which constitute a defense reaction to infectious microorganisms is required. However, the examiner merely speculates that such stimulation would be required. Applicants strongly disagree.

Applicants respectfully submit that it has never been suggested to treat an infection by microorganisms by injecting a pro-inflammatory agent to stimulate functions of neutrophils. Dr. Lipani has submitted his declaration in support of Applicants. Dr. Lipani has extensive experience as a medical practitioner and in research and development in the anti-inflammatory field. Dr. Lipani states that " there has never been even a hint of a suggestion that a doctor should treat an infection with fMLP. Indeed, such a treatment would aggrevate the pro-inflammatory response already caused by the infection and create further damage to tissue."

Thus, it is not seen how the present invention is anticipated or would have been obvious to one of ordinary skill in the art in view of Kermode.

Claims 1, 4-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kermode, as applied to claim 1 in the rejections above, and further in view of Goodman and Gilman. Goodman and Gilman are cited for teaching routes of administration and appropriate carriers. However, Goodman and Gilman do not make up for the deficiencies of Kermode. Goodman and Gilman do not teach or suggest the anti-inflammatory properties of the present invention.

Goodman and Gilman merely discuss the potential pros and cons of various routes of drug administration. Goodman and Gilman do not discuss **specific routes** of administration for **specific drugs**. Rather, they give a broad overview of drug administration and emphasize that there are many variables that influence the absorption, bioavailability and distribution of drugs. (See Goodman and Gilman pp. 4-5, 9.) One of the main features of the article is that **the drug itself** is a major reason for choosing a **specific route** of administration and no mention is made for administration of anti-inflammatory compositions. Furthermore, the appropriate carrier again depends on the composition of the drug. Thus the combination of references of Kermode, Goodman and Gilman do not teach or suggest the present invention. Accordingly, applicants request that this rejection be withdrawn.

In view of the amendment, the declarations of Dr. Clagett and Dr. Lipani, and the discussion above it is respectfully submitted that the present application is in condition for allowance. Early and favorable action is requested.

Respectfully submitted,

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